Cervical Adenocarcinoma and Squamous Cell Carcinoma Incidence Trends among White Women and Black Women in the United States for 1976–2000

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BACKGROUND. Although cervical carcinoma incidence and mortality rates have declined in the U.S. greatly since the introduction of the Papanicolaou smear, this decline has not been uniform for all histologic subtypes. Therefore, the authors assessed the differential incidence rates of squamous cell carcinoma (SCC) and adenocarcinoma (AC) of the cervix by race and disease stage for the past 25 years.
METHODS. Data from nine population-based cancer registries participating in the U.S. Surveillance, Epidemiology, and End Results (SEER) Program were used to compute incidence rates for cervical carcinoma diagnosed during 1976–2000 by histologic subtype (SCC and AC), race (black and white), age, and disease stage (in situ, localized, regional, or distant).
RESULTS. In black women and white women, the overall incidence of invasive SCC declined over time, and the majority of tumors that are detected currently are in situ and localized carcinomas in young women. The incidence of in situ SCC increased sharply in the early 1990s. AC in situ (AIS) incidence rates increased, especially among young women. In black women, invasive AC incidence rose linearly with age.
CONCLUSIONS. Changes in screening, endocervical sampling, nomenclature, and improvements in treatment likely explain the increased in situ cervical SCC incidence in white women and black women. Increasing AIS incidence over the past 20 years in white women has not yet translated into a decrease in invasive AC incidence. Etiologic factors may explain the rising invasive cervical AC incidence in young white women; rising cervical AC incidence with age in black women may reflect either lack of effective screening or a differential disease etiology. ***Cancer* 2004;100:1035–44.** © *2004 American Cancer Society.*

KEYWORDS: cervix, adenocarcinoma, squamous cell carcinoma, incidence, black, white, epidemiology.

Since the introduction of the Papanicolaou (Pap) test by Dr. George Papanicolaou in the 1940s, cervical carcinoma incidence and mortality rates have declined in the U.S. and in other developed countries.[1,2] Because most cervical carcinomas are squamous cell carcinomas (SCC), the decline in incidence and mortality largely can be attributed to the success of screening programs that detect preinvasive SCC. Conversely, a number of studies have now documented that incidence rates of the rarer cervical adenocarcinoma (AC) have been increasing in young women, particularly those born after the sexual revolution in the 1960s.[3–5] This trend has been reported in white populations of North America, Europe, and Australia and in non-white populations, including India, Japan, and Singapore.[3,6–12]

To date, reports from the U.S.-based Surveillance, Epidemiology,

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and End Results (SEER) Program registry have supported the observation of increasing cervical AC incidence rates in young white women[1,5,13] with further indication of a birth-cohort effect.[14] Given the simultaneous decline in SCC incidence, the resulting ratio of cervical AC to SCC has increased.[1,15] It is likely that the increasing AC incidence can be attributed in part to screening,[3] reflecting increased recognition and, thus, detection of AC lesions that previously were undiagnosed or were not categorized as AC. Although this is supported by a comparable decrease in the incidence of subtypes (specified and not otherwise specified [NOS]) other than SCC and AC,[1] it is not yet supported by increased rates of cervical AC in situ (AIS). Although recent studies have focused on AC, to our knowledge none published to date have compared the incidence of SCC with AC directly or have examined their relation to changes in screening practices. To assess the role of screening in cervical SCC and AC incidence rates in the U.S., we used the SEER registry database to determine cervical carcinoma incidence rates by histologic subtype, disease stage, race, age, and birth cohort. We used in situ carcinoma as a surrogate for screening effectiveness and assessed its impact on invasive carcinoma incidence rates for both SCC and AC. In the current report, we also discuss in depth the various events that have occurred during this time period, including changes in nomenclature, screening practices, endocervical sampling, and improved treatments.

MATERIALS AND METHODS

This analysis included data from nine SEER registries (San Francisco–Oakland, Connecticut, Detroit, Hawaii, Iowa, New Mexico, Seattle, Utah, and Atlanta). Details of the SEER Program, which represent approximately 10% of the U.S. population,[16] have been published previously.[17] Because reporting from all nine SEER sites did not begin until 1975, our analysis includes incident invasive cervical carcinoma cases diagnosed between 1976 and 2000. We include in situ cervical carcinomas diagnosed between 1976 and 1995, because reporting of in situ carcinomas ceased in 1996.[18]

Cervical carcinomas were identified using the International Classification of Disease for Oncology, 2nd edition (ICD-O-2) topography and morphology codes. Tumors diagnosed prior to 1992 originally were coded using ICD-O-1 and subsequently were recoded to ICD-O-2; tumors diagnosed 1992 and after were coded directly using ICD-O-2. We grouped tumors for analysis using a modification of the classification system proposed by Berg[19] in conjunction with the ICD-O-2 coding system.[20] Briefly, SCC was defined as ICD-O-2 codes 8050–8130, and AC was defined as ICD-O-2 codes 8140–8490. In addition, we defined adenosquamous carcinoma as ICD-O-2 codes 8560–8570; otherwise specified (OS) tumors were defined as ICD-O-2 codes 8720–8810 and 8910–8960; and NOS tumors were defined as ICD-O-2 codes 8000–8042, 8890–8900, and 8980–9581.

The SEER*Stat statistical software package (version 5.0.18) was used for all analyses.[21,22] Age-adjusted and age-specific incidence rates per 100,000 woman-years were calculated for in situ and invasive cervical carcinoma, using 10-year age intervals (15–24 years, 25–34 years, 35–44 years, 45–54 years, 55–64 years, 65–74 years, and $\geq$ 75 years), the U.S. standard, by race (white, black), histologic subtype (AC, SCC), and time period of diagnosis, and stage. The rates were plotted with the y-axis as incidence rate per 100,000 woman-years on a log scale, with age or year of diagnosis as the x-axis. The figures were prepared using the ratio of 1 log cycle to 40 years = 1, such that a slope of 10 degree represents an annual change of 1%.[23] According to the *SEER Summary Staging Manual*,[24] localized stage carcinoma is defined as invasive carcinoma confined to the cervix and corresponds to International Federation of Gynecology and Obstetrics (FIGO) Stages IA1, IA2, IB, and not further specified; regional carcinoma is defined as disease spread beyond the cervix by direct extension to adjacent organs or tissues and/or to regional lymph nodes and corresponds to FIGO Stages IIA, IIB, IIIA, IIIB, and III (NOS); and distant carcinoma is defined as disease with distant site(s)/lymph node(s) and corresponds to FIGO Stages IV, IVA, and IVB. In situ to invasive rate ratios and black-to-white rate ratios were calculated for each diagnostic year category.

RESULTS

A total of 27,016 incident invasive cervical carcinomas were diagnosed among white women and black women in the 9 SEER areas between January 1, 1976 and December 31, 2000. Of those tumors, 19,703 were SCC and 3895 were AC. The remaining were adenosquamous carcinomas (n = 956 tumors), carcinomas NOS (n = 2341 tumors), and carcinoma OS (n = 116 tumors). Overall, in situ SCC incidence among white women increased from 19.6 per 100,000 woman-years in 1976–1980 to 41.4 per 100,000 woman-years in 1991–1995 (Table 1), compared with decreasing incidence of invasive malignant SCC from 8.7 per 100,000 woman-years in 1976–1980 to 5.4 per 100,000 woman-years in 1996–2000; the in situ to invasive SCC rate ratio increased from 2.3 in 1976–1980 to 6.7 in 1991–1995. Among black women, in situ SCC rates declined from 24.8 to 14.7 per 100,000 woman-years in 1986–

TABLE 1
Age-Adjusted Surveillance, Epidemiology, and End Results Incidence Rates and Rate Ratios for In Situ and Invasive Cervical Carcinoma by Histologic Subtype, Race, and Year of Diagnosis[a]

	White					Black					Black:white rate ratio	
	In situ		Invasive		In situ invasive	In situ		Invasive		In situ invasive		
Year of diagnosis	Rate	Count	Rate	Count	rate ratio	Rate	Count	Rate	Count	rate ratio	In situ	Invasive
Squamous cell carcinoma												
1976–1980	19.6	8859	8.73	3660	2.25	24.77	1333	21.76	834	1.14	1.26	2.49
1981–1985	18.84	9391	7.15	3216	2.63	18.26	1108	16.25	723	1.12	0.97	2.27
1986–1990	21.23	11,098	6.89	3293	3.08	14.72	1028	13.19	667	1.12	0.69	1.91
1991–1995	41.44	21,748	6.19	3151	6.69	30.63	2421	10.6	640	2.89	0.74	1.71
1996–2000	—[b]	—[b]	5.37	2850	—[b]	—[b]	—[b]	9.63	669	—[b]	—[b]	1.79
Adenocarcinoma												
1976–1980	0.21	86	1.23	511	0.17	0.08	3	1.39	48	0.06	0.38	1.13
1981–1985	0.31	136	1.23	535	0.25	0.19	10	1.71	69	0.11	0.61	1.39
1986–1990	0.61	296	1.59	740	0.38	0.22	13	1.59	78	0.14	0.36	1.00
1991–1995	1.25	645	1.57	798	0.80	0.31	22	1.6	87	0.19	0.25	1.02
1996–2000	—[b]	—[b]	1.76	943	—[b]	—[b]	—[b]	1.36	86	—[b]	—[b]	0.77

[a] Per 100,000 woman-years (age-adjusted 2000 U.S. standard).
[b] Data for in situ carcinomas were not available.

1990 but increased sharply to 30.6 per 100,000 woman-years in 1991–1995. Because invasive SCC rates steadily declined over time from 21.8 to 9.6 per 100,000 woman-years, the resulting in situ-to-invasive rate ratio increased from 1.1 throughout 1976–1995 to 2.9 in 1991–1995. Invasive SCC incidence rates were higher in black women compared with white women, although the black-to-white ratios declined from 2.5 to 1.8. The black-to-white ratio for in situ SCC declined from 1.3 to 0.7 due to the more rapid increase among white women. AIS increased steadily among both white women and black women, and AC increased steadily among white women. The increase in AIS incidence outpaced that for AC, resulting in a rising in situ-to-invasive rate ratio among white women from 0.2 to 0.8. The rising AC rates among white women decreased the AC black-to-white rates from 1.1 to 0.8.

Age-adjusted localized, regional, and distant-stage SCC incidence rates declined from 1976–1980 to 1996–2000 in white women and black women, as did in situ SCC among black women until about 1990 (Fig. 1A and 1B). In situ SCC rates rose rapidly after 1990 in both groups. The incidence of in situ SCC was highest, followed by localized, regional, and distant-stage SCC. AIS incidence increased rapidly among white women and black women, as did the incidence of localized, regional, and distant AC among white women, but not among black women (Fig. 1C,D).

Incidence trends by period and age revealed that incidence rates of in situ SCC in white women increased steadily in women age ≥ 55 years. Although

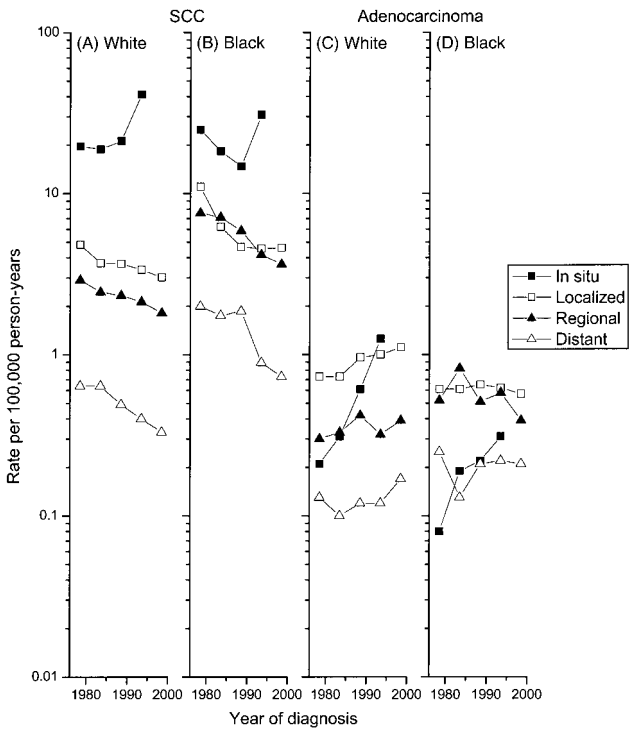

FIGURE 1. Age-adjusted (2000 U.S. standard) Surveillance, Epidemiology, and End Results (SEER) incidence rates for cervical carcinoma by histologic subtype, race, stage, and year of diagnosis (1976–1980 and 1996–2000): (A) Squamous cell carcinoma (SCC) in white women. (B) SCC in black women. (C) Adenocarcinoma in white women. (D) Adenocarcinoma in black women (in situ data to 1995).

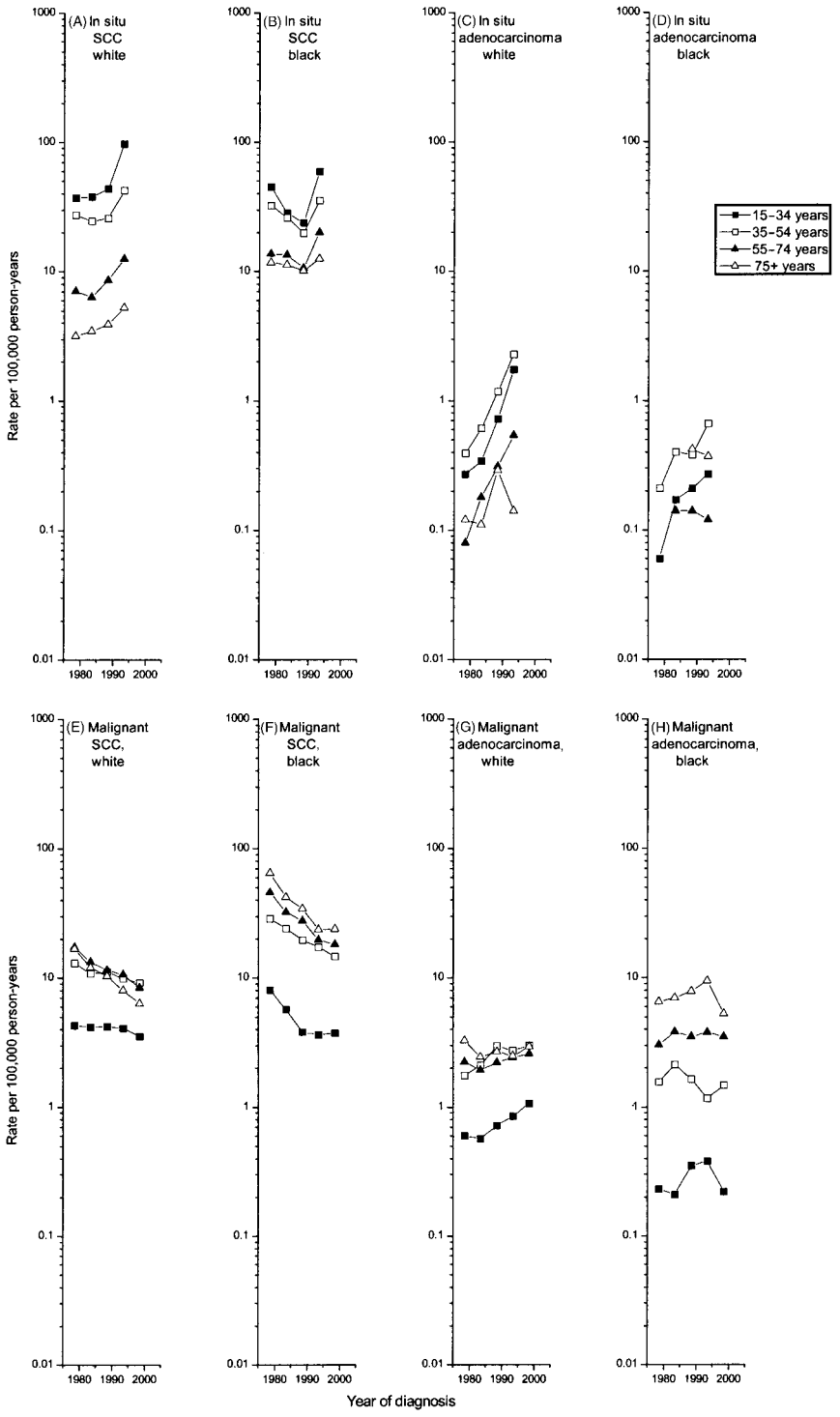

FIGURE 2. Incidence rates for in situ and invasive cervical carcinoma between 1976 to 1995 by histologic subtype, race, and age: (A) In situ squamous cell carcinoma (SCC) in white women. (B) In situ SCC in black women. (C) Adenocarcinoma in situ (AIS) in white women. (D) AIS in black women. (E) Invasive SCC in white women. (F) Invasive SCC in black women. (G) Invasive adenocarcinoma (AC) in white women. (H) invasive AC in black women.

this increase was not as clear for women age < 55 years, there was a sharp and notable increase in incidence in 1992–1993 (Fig. 2A). In situ SCC rates for black women (Fig. 2B) demonstrated this same increase in 1992–1993. A steady increase in incidence for in situ SCC was observed for black women age ≥ 55 years.

AIS appeared to increase steadily over time for white women ages 15–74 years (Fig. 2C). Although numbers were sparse, in black women, the increase

was milder and appeared to be limited to women ages 15–54 years (Fig. 2D). Rising in situ SCC rates corresponded to decreasing invasive SCC rates (Fig. 2E,F); the age group with the highest in situ SCC incidence rates (e.g., ages 15–34 years) also had the lowest invasive SCC rates. Conversely, increasing AIS incidence in white women did not correlate with decreasing AC, and those age groups with the highest in situ incidence rates (e.g., ages 35–54 years) did not appear to have the lowest invasive AC incidence rates (Fig. 2G,H). A steady increase in incidence clearly was observed for invasive AC in white women ages 15–54 years. Although numbers were very small and unstable, the incidence of invasive AC in black women did not alter significantly over time.

Age-specific invasive SCC incidence rates declined from 1976–1987 to 1988–2000 among both white women and black women, especially among women age $\geq$ 45 years (Fig. 3A and 3B). Rates remain higher in black women compared with white women, particularly among women age $\geq$ 35 years. Invasive AC incidence rates increased in white women age $<$ 65 years (Fig. 3C), but the rates did not change greatly among black women (Fig. 3D). The age-specific rates for AC in white women and for SCC among both white women and black women rose sharply among younger women and plateaued after $\approx$ age 35 years. In contrast, AC rates in black women increased steadily with age, with no signs of plateauing.

The age-specific incidence rates during 1976–2000 by stage reveal clear screening effects for SCC. In situ SCC rates were highest in the targeted screening ages of 25–34 years (Fig. 4A,B). Incidence rates for localized tumors were lower than for in situ tumors, lower still for regional tumors, and lowest for distant tumors, each peaking at progressively older ages. In situ SCC rates were higher among white women compared with black women, especially at young ages, and distant-stage disease rates were higher in black women compared with white women, especially at older ages. AIS rates were much lower than SCC in situ rates at all ages. AIS rates peaked at ages 35–44 years among both white women and black women, as did the rates for localized AC among white women (Fig. 4C and 4D). Notably, rates for regional and distant-stage AC among white woman and AC of all stages among black women increased with age.

DISCUSSION

The data presented from the past 25 years of incidence reporting by 9 SEER registries demonstrate a clear screening effect on SCC of the cervix in white women and black women. The high incidence of in situ SCC in young women reflects a displacement of invasive SCC at older ages. Stepwise decreases in incidence for each advancing stage of invasive tumor were observed. Over time, rates for all stages of invasive SCC appear to have decreased, whereas in situ SCC rates increased.

For black women, it is unclear why the incidence of in situ SCC decreased from 1976–1990 before increasing from 1991–1995; this may be the expected temporal delay prior to the observed effects of screening. Despite the screening-associated stage shift, invasive SCC incidence rates among black women still exceeded those among white women. If effective screening for black women was received more recently than for white women, as the delay in rising in situ SCC rates suggests, then the higher incidence rate of invasive SCC among black women is expected. Although numerous surveys have reported similar Pap screening practices between white women and black women,[25,26] these differential rates still may be due to differences in the quality of screening and subsequent management of cases. Finally, potential differences in risk factors for SCC by race cannot be excluded.[27,28]

We noted a sharp increase in incidence in the early 1990s for in situ SCC in both white women and black women. Several events may have contributed to this dramatic increase: nomenclature and classification due to the introduction of The Bethesda System in 1988–1989 and its subsequent revision in 1991,[29] the introduction of the Clinical Laboratory Improvement Act of 1988 (CLIA '88), the CDC nationwide National Breast and Cervical Cancer Early Detection Program,[30,31] and the widespread introduction and use of the loop electrosurgical excision procedure (LEEP).

During the 25 years that were included in this analysis, the classification of cervical neoplasia evolved from the histologic classification of carcinoma in situ to cervical intraepithelial neoplasia (CIN). Thus, the nomenclature varied by participating SEER laboratories, as did their reporting in the SEER registry. In 1988, The Bethesda System, which was developed in 1988 and revised in 1991,[29,32,33] created the histology subtype *high-grade squamous intraepithelial lesions*, which encompassed CIN2, CIN3, and carcinoma in situ. The Bethesda System, therefore, would refer more women for colposcopy, potentially leading to an increase in the number of women diagnosed with in situ carcinomas.[34,35] The number of in situ diagnoses in SEER would have increased if laboratories had switched uniformly to this system in the early 1990s. Although this may impact rates, other factors probably are important, because not all laboratories use The Bethesda System.

The CLIA '88 implemented proficiency testing for laboratories that interpret cervical cytology smears. By

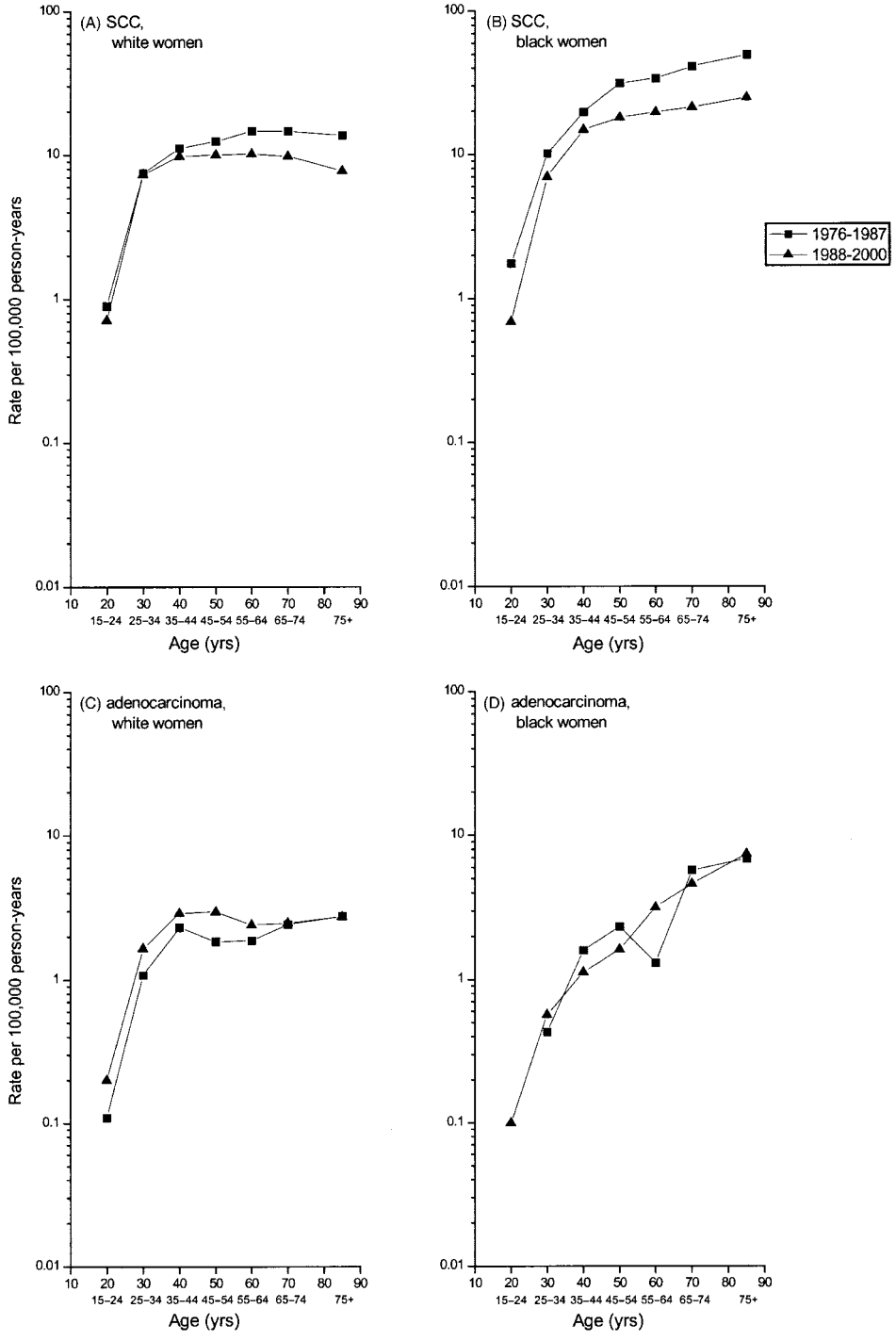

FIGURE 3. Age-specific Surveillance, Epidemiology, and End Results (SEER) incidence rates for cervical carcinoma by histologic subtype, cohort, and race (1976–1987 and 1988–2000): (A) Squamous cell carcinoma (SCC) in white women. (B) SCC in black women. (C) Adenocarcinoma in white women. (D) adenocarcinoma in black women.

imposing limits on the number of Pap smears read each day[36] to reduce the number of false-negative results, this act also may have increased in situ incidence rates in the early 1990s.[37]

Nationwide screening programs also may have contributed to this period effect. The Centers for Disease Control (CDC) National Breast and Cervical Cancer Detection Program was initiated in 1991 and was implemented nationwide by 1995. Intended to improve screening compliance in historically underscreened populations, this program may have contributed to the in situ rates in black women.[38–40]

Finally, the LEEP was introduced in the 1980s and was adopted by gynecologists worldwide by 1990.[41]

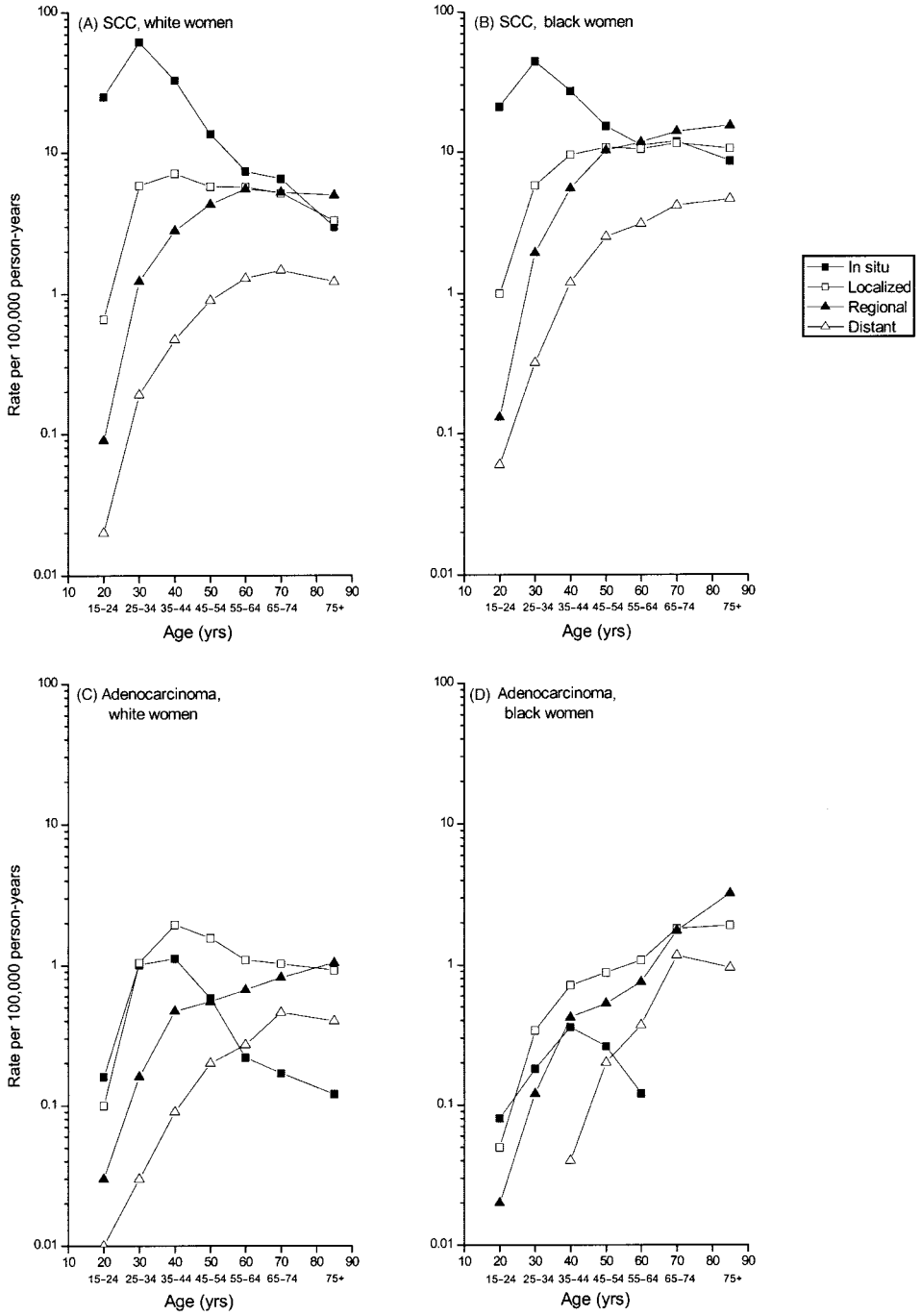

FIGURE 4. Age-specific Surveillance, Epidemiology, and End Results (SEER) incidence rates for cervical carcinoma by histologic subtype, stage, and race (1976–1987 and 1988–2000): (A) Squamous cell carcinoma (SCC) in white women. (B) SCC in black women. (C) Adenocarcinoma in white women. (D) Adenocarcinoma in black women.

Prior to the use of LEEP, patients with carcinoma in situ underwent cone biopsy or hysterectomy; this made a conservative definition of a precursor lesion desirable. Treatment by LEEP allowed CIN removals to take place in an outpatient or office setting. This new and improved treatment option potentially may have led to an increased number of women being referred for colposcopy, thus contributed to the increased number of women diagnosed with in situ carcinomas. This also would lead to a more accurate classification of disease and would be more likely to have been recorded in SEER.

The expected effect of screening is not yet evident as a decline in AC incidence rates. Despite increasing AIS incidence rates over the past 25 years in white women of all age groups, invasive AC incidence rates have not appeared to decline. In fact, invasive AC rates appear to have increased, predominantly in young

white women. This observation is consistent with a previous SEER analysis conducted by Zheng et al. in 1996 that demonstrated a birth-cohort effect.[14] Possible reasons for the increase in invasive AC in white women include the increased recognition and awareness of AC, which lead to an increased number of referrals. Cytomorphology of AIS also became better described in late 1980s and 1990s, likely contributing to the increase of AIS in all age groups. During that time, endocervical sampling techniques for Pap smears improved greatly[42]; and new sampling devices, such as endocervical brush and broom, enhanced collection of cells from the upper portion of the endocervical canal,[43] leading to improved detection of AC lesions and contributing to the observed increase in the incidence of earlier stage invasive AC.[44] Nomenclature changes that may have affected reporting of in situ SCC are not likely to impact AC in the same manner. For AC, there is one precursor lesion (AIS), diminishing the potential for misclassification; nevertheless, we cannot dismiss potential misclassification between AIS and early invasive AC.[4] Some variation also may be attributed to the current ability to recognize other subtypes as AC.[1] Finally, issues related to treatment for AIS and AC most likely are relevant; unlike SCC, to our knowledge there are no simple outpatient treatments for patients with AIS and AC, for whom surgery (e.g., cold knife cones or hysterectomies) is standard. Therefore, the advantage afforded to detection and treatment of in situ SCC, which is reflected by the in situ and invasive SCC rates, may not result in the same patterns of AIS and AC reporting for incidence and histologic SEER reporting.

If improved surveillance, differential classification, and a cohort effect do not explain entirely the rise of AC in young white women,[14,45] then etiologic reasons must play a role. Potential risk factors for AC that have increased in prevalence over this period include nulliparity and obesity.[46–50] Although oral contraceptive (OC) use peaked in women who were in their 20s and 30s during the early 1960s in developed countries[46] and reportedly has increased the risk of AIS,[51] OC formulations have changed over time, and it remains unclear how this may impact incidence rates. The trend of women having fewer children at older ages is associated with increased risk for AC and, thus, also may contribute to the simultaneous rise in invasive AC, particularly in recent cohorts.[47] The obesity epidemic among women in the U.S. may contribute to a hormonal etiology and also is hypothesized to interfere with effective screening, thus complicating detection.[50] Finally, although human papillomavirus 18 (HPV-18) is the HPV type associated most with AC, it is unclear whether its prevalence has changed in the last 25 years.[3,47] Because of the relatively modest risk estimates observed to date, these risk factors most likely would not affect incidence trends significantly on their own but may do so together.

The striking linear increase in age-specific incidence rates for invasive AC among black women, compared with the plateau among white women, suggests a different disease etiology and/or lack of effective screening and treatment. Recent surveys indicate that nulliparity and OC use are higher in white women compared with black women.[52] Although we cannot rule out the potential for a hormonal role, it appears that added difficulties in screening as well as physiologic effects related to obesity may be differential between black women and white women[53] and, thus, potentially play a role in the differential rates of invasive AC in black women; recent national data indicate a higher prevalence of obese and overweight black women compared with white women.[54] Currently, it is unknown whether HPV-18 infections or their subtypes vary by race; however, as stated earlier, it is likely that these risk factors act in concert and that any one risk factor (e.g., obesity) may be enhanced by the presence of other risk factors.

Although numerous surveys have indicated similar Pap smear screening practices among black and white women in the U.S.,[25,55–57] the quality of screening may differ by race and socioeconomic status. If differences within the three SEER registries are present, and if screening quality differs, then it is possible that their effects would manifest in a rare and difficult to sample tumor, such as cervical AC; differences also may be reflected by the higher SCC rates in black women compared with white women. However, if cervical sampling, in fact, is equivalent in black and white women, then the possibility of etiologic differences between AC in black and white women must be considered. Furthermore, because SCC rates plateaued after ages 45–50 years even before screening, it is possible that true etiologic differences are more likely to explain this finding rather than screening differences and changes.

Despite the noted limitations in the reporting of in situ carcinoma between SEER registries from changing terminology and practices over time, as well as the assumptions made between detection of preinvasive lesions through cytology and SEER reporting by histology, our results for in situ and invasive SCC appear to reflect accurately the expected association between in situ and invasive carcinomas[28] with regard to time and age. Coupled with data regarding disease stage, our rates appear to reflect the expected effects of screening. Although we did not adjust for hysterectomy rates in the current analyses, the rates likely

would increase, because the total woman-years would decline. In addition, it is believed that hysterectomy rates would have less impact because, increasingly, LEEP or localized treatment is now the norm. Furthermore, more recent data suggest equivalent hysterectomy rates among white women and black women.[58]

In the current analysis, we confirmed the continuing decline in invasive SCC in U.S. women. This clearly is attributable to screening. We hypothesize that the period effect of increased in situ SCC observed in the early 1990s is due to a culmination of events, including changes in nomenclature, improvements in treatment, and screening. There appears to be a greater screening effect in white women compared with black women; this discrepancy most likely is attributable to differences in screening quality. Although screening, improved endocervical sampling, and increased recognition of AC have resulted in increased AIS incidence rates in white women, to our knowledge invasive AC incidence rates still have not decreased. We further confirm the increase of AC in young white women; although different etiologies, such as increasing obesity and nulliparity, may contribute to the increase in recent cohorts, the roles of the main viral factor, HPV-18, and of changing OC formulations to our knowledge remain unknown. Although there does not yet appear to be a screening effect for invasive AC, sufficient time may not have lapsed for an effect to be observed.[59] The small numbers of AC lesions likely will require a longer time before the effects of screening will affect reported SEER rates. Further studies investigating the survival of women with AC will be beneficial for assessing potential screening effects on AC.[60]

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